

Study of Incidence and Factors Affecting Morbidity and Mortality in Patients of Pancreaticoduodenectomy

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ABSTRACT

Background: Whipple Pancreaticoduodenectomy (PD) is a technically challenging surgery. Even though the mortality has decreased to 2-10%, the morbidity still remains high with 40-60% in most of the centers. The purpose of the present study is to analyze the incidence and risk factors affecting the morbidity and mortality in patients undergoing pancreaticoduodenectomy and to compare the obtained data with the literature. **Methods:** A retrospective review of prospectively maintained database of 85 patients with obstructive jaundice was done from October 2013 to September 2018 out of which 57 (67%) patients were operable and underwent PD. These 57 patients were included in our study. 28 (33%) patients were inoperable out of which 16 (57.1%) underwent palliative CBD stenting and 12 (42.9 %) underwent triple bypass. **Results:** Out of 57 operated patients 40 patients were males and 17 females with a mean age of 55.35 years (range, 21-78 years). 28 patients (49.1%) underwent preoperative biliary drainage, with the insertion of biliary stents in 25 patients through ERCP, 2 underwent percutaneous transhepatic tube cholecystostomy and 1 underwent t-tube drainage of CBD. Periampullary adenocarcinoma was seen in 53 patients, 2 had neuroendocrine tumour and 2 had cystic neoplasm of head of pancreas. Bilirubin > 10 mg/dl was noted in 42 patients (73.68 %), hypoalbuminemia (< 3.5 gm/dl) was seen in 25 patients (43.8 %), and pancreatic duct diameter < 3mm was seen in 26 patients (45.6 %). On analysis of drain fluid amylase on post-operative day 3, 5 and 7, Postoperative pancreatic fistula was noted in 26 patients (45.6%), out of which 10 patients (17.5%) had clinically relevant post-operative pancreatic fistula (CR-POPF). Abdominal sepsis was seen in 5 patients(8.7%), DGE in 4 patients(7%), SSI in 3 patients(5.2%), post-operative haemorrhage in 3 patients (5.2 %), bile leak in 1 patient(1.7%). Re exploration was needed in 5 patients, out of which 2 patients were re-explored for pancreatic leak and 3 patients were re-explored for post-operative haemorrhage. Postoperative mortality was seen in 6 patients. Overall morbidity and mortality was 45.6% and 10.52% respectively. On Bivariate analysis CR-POPF (p value=.0024), diabetes (p value=0.0305), hypoalbuminemia (p value=0.0127) and intra operative blood loss >600ml (p value=0.014) were significant factors for morbidity and mortality in present study. **Conclusion:** In this study we have demonstrated that CR-POPF, DM, hypoalbuminemia, high intraoperative blood loss and preoperative biliary drainage increase post operative morbidity and mortality.

Keywords: morbidity, pancreaticoduodenectomy, postoperative pancreatic fistula.

Abbreviations: CR-POPF= clinically relevant post-operative pancreatic fistula, CBD=common bile duct, DGE= delayed gastric emptying, PD=pancreaticoduodenectomy, PJ=pancreaticojejunostomy, POPF=postoperative pancreatic fistula, SSI= surgical site infection

INTRODUCTION

Pancreaticoduodenectomy (PD) is one of the most technically challenging and complex operation performed for managing various benign and

malignant diseases including trauma of periampullary region.^[1] This procedure was first described by Whipple et al in 1935, with the mortality rate more than 30%. Due to marked progress in the procedure, nutrition and, anaesthesia the mortality rate is reported to be 2%-10% in most hospitals.^[2,3] PD being a technical challenge to surgeons also remains the only hope for cure in patients with cancer at periampullary region.^[4,5] Though Alessandro Codivilla was the first person to perform a PD,^[6] it was Allen Whipple who

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popularized this surgery.^[7] Pancreatic surgery has advanced considerably during the past two decades with several modifications have been reported, including the pylorus-preserving pancreaticoduodenectomy (PPPD).^[8,9] Several studies and reviews have reported similar outcomes in terms of delayed gastric emptying, post operative nasogastric drainage, blood loss, hospital stay, long term survival and disease free survival between Classical PD and PPPD.^[10,11] In this era with intensive care units, safer general anaesthesia and computed tomography incorporated into clinical care has made the mortality to decrease up to 10% or less, but still the morbidity continues to remain high up to 40-60%.^[12-18]

In this study we intend to discuss various factors affecting mortality and morbidity in patients undergoing pancreaticoduodenectomy.

MATERIALS AND METHODS

A retrospective review of prospectively maintained database of 85 patients with obstructive jaundice was done from October 2013 to September 2018 at NHL Municipal medical college, Ahmedabad, India. This study included fifty seven patients with resectable tumour who underwent classical pancreaticoduodenectomy in our institute. Twenty eight patients undergoing palliative CBD stenting or triple bypass were excluded in present study as they were inoperable. Preoperative work up consisted of detailed history and clinical examination, resectability was determined by ultrasound examination, CECT, tumour markers (CEA and CA19-9), side viewing scop and preoperative biopsy as and when needed. Preoperative fitness was

evaluated with routine investigation and preoperative optimization was done for patients who were not fit for surgery at admission. Preoperative biliary drainage was done for patients with bilirubin more than 15mg/dl and cholangitis. Patients with failed ERCP were subjected to surgical drainage and percutaneous transhepatic tube cholecystostomy. All patients were explored using bilateral subcostal or Mercedes Benz incision. Dissemination of disease is checked by manual palpation, IOU and frozen section if required. In any evidence of metastasis procedure was abandoned. Rest patients underwent classical PD. In all patients artery first approach was used. Reconstruction comprised end to side PJ (ducto-mucosa pancreatico jejunal anastomosis), Hepaticojejunostomy and antecolic gastrojejunostomy. In all patients external pancreatic stent was kept. All vessels were suture ligated and no staplers were used for anastomosis. Two abdominal drains were placed, one near PJ anastomosis and another near HJ anastomosis. Standard Post-Operative Care included nasogastric tube for gastric decompression for every patient. Feeding was started from day 1 with glucose water through FJ and day 4 per orally. Nasogastric tube was removed if patient tolerate oral feeds on day 4. Patient was mobilised from day 1. Foleys catheter removed on day 2 if patient do not require ICU admission. Drains were removed on day 8 of surgery if there was no evidence of pancreatic fistula. All patients were given injection octreotide 100 microgram subcutaneously thrice a day for 5 days. Amylase levels were monitored in the intraoperative placed abdominal drains on 3rd, 5th and 7th day after surgery.

Table: International Study Group for Pancreatic Surgery grading of Postoperative pancreatic fistula after pancreatic surgery

Grade A	Transient fistula	No clinical impact	No peri-pancreatic collections on CT scan; little/no change in management	Clinically well; no sepsis; no prolongation of hospital stay; slow removal of operatively placed drains
Grade B		Clinical impact Present	Peri-pancreatic drains in place or repositioned to drain collections; Change in management	Clinically fairly well; degree of infection requiring specific treatment; prolongation of hospital stay; patients often discharged with drains in situ and observed in outpatient setting
Grade C		Severe clinical impact	Worrisome peri-pancreatic collections that require percutaneous drains; major change in management usually in ICU setting; possible re-surgery to salvage a difficult situation (completion pancreatectomy etc)	Clinically unwell; associated sepsis requiring aggressive antibiotics, octreotide and other intensive care support; major prolongation of hospital stay; associated complications and possibility of mortality

Pancreatic fibrosis scale was devised-

	Fibrosis	Lobular changes	Inflammation	Lobule changes	Duct changes
1	Little	Focal perilobular fibrosis	Focal	Atrophy of normal lobe	Mild duct ectasia
2	Moderate	Intralobular fibrosis with septa	Moderate	Focal atrophy of lobule	Moderate duct ectasia
3	Severe	Generalised fibrosis, destruction of acini	Extensive	Total atrophy of lobe	Intense duct ectasia

Classified:

- I - normal pancreas or with mild fibrosis (0-4 points);
- II - pancreas with moderate fibrosis (5-10 points);
- III - pancreas with severe fibrosis (11- 15 points).

Statistical analysis

All continuous variables were expressed as a mean and standard deviation (SD) and compared using the Student's t test. Bivariate analysis was done. Categorical variables were compared using the Chi squared test with Fisher's exact test to evaluate the impact of clinical and operative parameters. Statistical analysis was performed using graphpad.com. A P value 0.05 was considered statistically significant.

RESULTS

From October 2013 to September 2019, 85 patients with periampullary tumours were admitted in NHL Municipal Medical college and Hospital out of which 57 (67%) patients were operable and underwent PD; 28 (33%) patients were inoperable out of which 16 (57.1%) underwent palliative CBD stenting and 12 (42.9 %) underwent triple bypass. All operable patients were operated and managed by a team of surgeons specialized in hepatopancreaticobiliary (HPB) surgery.

Out of 57 operated patients there were 40 males and 17 females. The mean age of male was 56.31 years and female was 55.4 years with overall mean age of 55.35 years (range, 21–78 years). 19 patients (33.3 %) were elderly, aged more than 65 years. 36 (63.1%) patients had one or more chronic co-morbid illnesses, out of which diabetes mellitus was seen in 17 (47.2%) and hypertension in 15 (41.6 %). 28 patients (49.1%) underwent preoperative biliary drainage, with the insertion of biliary stents in 25 patients through ERCP, 2 underwent cholecystostomy and 1 underwent tube drainage.

The average BMI was 27.11. Average blood loss was 502.45ml. Average duration of surgery was 5.95 hours.

53(92.9%) patients had periampullary adenocarcinoma, 2(3.5%) had neuroendocrine tumour and 2(3.5%) had cystic neoplasm of pancreas. 20 (35%) patients had soft pancreas and rest 37 patients (65%) were having firm pancreas. Billirubin > 10 mg/dl was noted in 42 patients (73.68 %), hypoalbuminemia (< 3.5 gm/dl) was seen in 25 patients (43.8 %), and pancreatic duct diameter < 3mm was seen in 26 patients (45.6 %). POPF was noted in 26 patients (45.6%), out of which 10 patients (17.5%) had CR- POPF, abdominal sepsis was seen in 5 patients (8.7%), DGE in 4 patients (7%), SSI in 3 patients (5.2%), post operative haemorrhage in 3 patients (5.2 %), and bile leak in 1 patient (1.7%).

Table 1: Result in Number and Percentage

Results	In Numbers	In Percentage
NUMBER OF PATIENTS	85	
OPERABLE	57	67.0%
NON OPERABLE	28	33.0%
STENTED	16	57.1%
TRIPLE BY PASS	12	42.9 %
MALE	40	70.1 %
FEMALE	17	29.9%
MEAN AGE	55.35 YRS	
RANGE	21-78	
>65 YRS	19	33.3 %
<65 YRS	38	66.66 %
Average BMI	27.11	
< 25	21	
> 25	36	
CO MORBIDITIES	36	63.1 %
DM	17	47.2 %
HTN	15	41.6 %
COPD	4	11.1 %
PRE OP BILLIARY DRAINAGE	28	49.1 %
ERCP + STENTING	25	89.2 %
CHOECYSTOSTOMY	2	7.1 4 %
T TUBE DRAINAGE	1	3.57 %
AVG BLOOD LOSS	502.425 ml	
> 600 ml	15	26.31 %
< 600 ml	42	73.64 %
DURATION OF SURGERY	5.95 HRS	
ADENOCARCINOMA	53	93 %
NEUROENDOCRINE TUMOR	2	3.5 %
CYSTIC NEOPLASM OF PANCREAS	2	3.5 %
PANCREATIC TEXTURE		
SOFT PANCREAS	20	35.08 %
FIRM PANCREAS	37	64.91 %
PANCREATIC FIBROSIS		
GRADE I	20	35.08 %
GRADE II	17	29. 82 %
GRADE III	20	35.08 %
BILLIRUBIN in mg/ dl		
> 10	42	73.68 %
< 10	15	26.31 %
SERUM ALBUMIN IN gm / dl		
< 3.5	25	43.8 %
> 3.5	32	56.1 %
MPD DIAMETER IN MM		
< 3 mm	26	45.6 %
> 3 mm	31	54.3 %

Table No 2: Post Operative Morbidity

COMPLICATIONS	n	n x 100/ total operated cases
POPF (TYPE A+ B + C)	26	45.6 %
POPF TYPE A	16	22.8 %
CR- POPF (TYPE B + C)	10	17.5 %
BILE LEAK	1	1.7 %
INTESTINAL LEAK	0	0
HAEMORRHAGE	3	5.2 %
DGE	4	7 %
ABDOMINAL SEPSIS	5	8.7 %
SSI	3	5.2 %
RE EX LAPAROTOMY	5	8.7 %

5 patients underwent re-exploration. Peritoneal lavage and drainage was done in 2 patients re-explored for pancreatic leak. Rest 3 patients were re-explored for post operative haemorrhage. Post operative haemorrhage due to pseudo aneurysm of

gastrooduodenal artery was seen in 1 patient, 1 patient had haemorrhage from pancreaticoduodenal branch of aberrant right hepatic artery and 1 patient had haemorrhage from tip of pancreatic stump. Postoperative mortality was seen in 6 patients. 5

patients died due to severe sepsis following CR POPF and 1 patient died due to post operative haemorrhage from pancreaticoduodenal branch of aberrant right hepatic artery. Overall all morbidity and mortality was 45.6 % and 10.52% respectively.

Table 3: Bivariate Analyses (Fisher's Exact Test With Two Tails) Of Mpd Diameter And Pancreatic Texture With Popf And Cr-Popf (Grade B + C)

Sr. No.	FACTORS	POPF (GRADE A+ B + C)			CR-POPF (GRADE B + C)		
		YES	NO	P VALUE	YES	NO	P VALUE
1	MPD DIAMETER in mm < 3 mm > 3 mm	19 7	7 24	0.0002	8 2	18 29	.034
2	PANCREATIC TEXTURE SOFT FIRM	16 10	4 27	0.0002	8 2	12 35	0.0021
3	DIABETES YES NO	12 14	6 25	0.044	7 3	11 36	0.0075

Table No 4: Bivariate Analyses (Fisher's Exact Test With Two Tails) For Factors Affecting Morbidity And Mortality

SL NO	FACTORS	MORBIDITY			MORTALITY		
		YES	NO	P VALUE	YES	NO	P VALUE
1	AGE >65 YRS (n= 19) <65 YRS (n= 38)	SEPSIS 4 1	SEPSIS 34 18	0.65	4 2	34 17	1.0
2	BMI <25 >25	Sepsis 1 4	Sepsis 20 32	0.617	2 4	19 32	1.0
3	DIABETES YES NO	Sepsis 4 1	Sepsis 14 38	0.0305	5 1	13 38	0.009
4	BILLIRUBIN mg/ dl > 10 < 10	Sepsis 4 1	Sepsis 38 14	1	4 2	38 13	0.64
5	Serum albumin < 3.5 > 3.5	Sepsis 5 0	Sepsis 20 32	0.0127	6 0	19 32	0.049
6	BLOOD LOSS in ml > 600 ml < 600 ml	Sepsis 4 1	Sepsis 11 41	0.014	4 2	11 40	0.036
7	CR-POPF YES NO	Sepsis 4 1	Sepsis 6 46	0.0024	4 2	6 45	0.006
8	BMI < 25 > 25	Sepsis 1 4	Sepsis 22 30	0.638	2 4	19 32	1
9	PRE OP ERCP+STENTING STENTED NOT STENTED	Blood Loss>600 Ml 11 4	Blood Loss <600 Ml 14 28	0.013	4 2	21 30	0.3883

DISCUSSION

Pancreaticoduodenectomy is a well accepted surgery now-a-days. In various studies the overall morbidity of 40-65% and mortality of 5-10% in pancreaticoduodenectomy has been reported.^[19-21] Salvatore et al (2017),^[22] and Narongsak Rungsakulkij et al (2019),^[23] reported a morbidity 61.8% and 65.97% respectively with POPF being the most common cause. In our study we had morbidity and mortality of 45.6% and 10.5% respectively, CR- POPF being the leading cause 17.8 %, which was in accordance to present literature [Table 2].^[18, 24]

PJ anastomosis i.e. "Achilles heel of pancreatic surgery" has been dependent upon various factors.

Soft texture of gland, small mpd <3mm and less gland fibrosis have been shown as independent risk factors in various studies but BMI>25kg/m², hypoalbuminemia, intraoperative blood loss, age, co morbidities and PBD are controversial for POPF.^[26-34] In accordance with the literature, in our study the incidence of pancreatic fistula was significantly higher in patients pancreatic duct diameter less than 3mm (p value= 0.034), soft pancreatic texture (p value= 0.0021) and DM (p value = 0.0075). [Table 3]

The effect of BMI >25 kg/m² in pancreatic surgeries has been studied by various groups. Some investigators have concluded that a high BMI is directly related to softness of pancreas and independent risk factors for CR-POPF.^[18,26,31-34]

Sandini et al. reported that, rather than BMI, the distribution of excessive abdominal fat, measured by preoperative CT, is a strong risk factor for POPF.^[30] In our study BMI was statistically insignificant for causing sepsis (p value =0.61) and mortality (p value =1) [Table 4]

Delayed gastric emptying incidence is seen in patients undergoing pancreatico-duodenectomy with incidence of 7.3%-12.3%.^[33] Recent studies seem to support that the incidence rates of DGE following either PD or PPPD are comparable. DGE remains a leading cause of postoperative complications and prolonged hospital stay.^[33] In our study, the incidence of DGE was 7.0 % and was comparable with the most of the series in the literature. [Table 2] Elderly population, age >65 years is a known risk factor for any type of major surgery due to decrease physiological reserve.^[22,36] Various studies has proved the relation of fatty pancreas in older age and increased leak rate.^[35] In the study of Martin AN et al age was significant independent risk factor for POPF,^[31] however other studies age was insignificant.^[18,24,30,32,34,37] As, the biological status cannot be defined by a number and the decision to submit to surgery elderly patients must be weighed over the risks considering multiple factors (co morbidities, performance status, patient choice, home assistance, life expectancy).^[22] In our study age was not statistically significant for sepsis (p=0.65) and mortality (p value =1) [Table 4]

Lyu et al reported that preoperative serum albumin < 3.5 mg/dL was a predictor for unplanned 30 days reoperation. Moreover, Agustin et al reported that serum albumin < 3.5 g/dL was an independent factor associated with Clavien-Dindo grade IV complications and mortality in the pancreatic surgery patients. Hypoalbuminemia being an independent risk factor for POPF is also been shown in various studies.^[28,37,38] However hypoalbuminemia was statistically insignificant in other studies.^[18,34,36,39] In our study 25 (43.8%) patients had hypoalbuminemia out of which 8 patients had CR-POPF, 5 developed sepsis and mortality was seen in 6 patients According to these reports, we conclude that preoperative hypoalbuminemia is a significant risk factor for serious postoperative complications e.g. sepsis (p value =0.012) and mortality (p value=0.049), especially after pancreatic resection.[Table 3]

Uncontrolled Diabetes mellitus is known for causing various morbidities in post operative period especially SSI and intra abdominal sepsis. In some studies diabetes mellitus was significant risk factor for POPF,^[24,31] and in some it was insignificant.^[24,31,32,38,39] In our study DM was significant factor for POPF, CR-POPF, sepsis (p value =0.03) and mortality [Table 3 & 4].

Preoperative biliary drainage has been a controversial issue for some time. Indications for stenting are severe cholangitis not responding to

antibiotics, severe nutritional deficiency and coagulopathy.^[40] Proponents of stenting are of the opinion that normobillirubinemia improves the nutritional status, healing process, immunity. It prevents coagulopathy; cholangitis and endotoxemia therefore there are overall less major adverse events compared to the direct surgery group.^[41] Van der Gaag,^[42] and colleagues found the overall post operative complication rates to be 39% in the non stented and 74% in the stented group with morbidity attributed to stenting in 37% and to the resection in 47%. Furthermore, three meta-analyses have recently been published all of which concluded that pre-operative biliary drainage offers no benefit and as such should not be performed routinely.^[41,43] In our study billirubin > 10 mg/dl was not significant risk factor for, sepsis (p value =1) or mortality (p value =0.64), however it resulted in increased intraoperative blood loss, reoperations and prolonged hospital stay. [Table 4]

Intraoperative blood loss and its effects on post-operative period has been a constant area of ongoing research. Investigators have proposed that, advanced pancreatic disease patients usually have intraoperative blood loss exceeding 1,500 ml and they are at higher risk of fistula development.^[44,45] In the study of Patel A C et al,^[30] Yoshito tomimaru et al,^[18] and Kazanjian et al,^[46] intra operative blood loss of >1000ml, 850 ml and 490 ml respectively were insignificant. In our study blood loss was significant factor for morbidity (p value =0.014) and mortality (p value=0.03). [Table 4]

CONCLUSION

Whipple pancreaticoduodenectomy can be performed safely at experienced hepatobiliary center with acceptable morbidity and mortality. Patient, surgeon and intraoperative factors are all important in addressing the post operative morbidities in PD. POPF is a dreaded complication of pancreatic surgeries and its prediction and prevention remains an area of debate. In this study we have demonstrated that CR-POPF, DM, hypoalbuminemia, high intraoperative blood loss and preoperative biliary drainage increase post operative morbidity and mortality. Randomized, controlled trials with larger cohorts are required to further validate the findings of this study.

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